IN THE DRAWINGS:

Accompanying this Amendment are the attached sheets of drawings that include changes to FIGS. 4, 8, and 10. These sheets, which include FIGS. 4, 8, and 10, replace the original sheets including FIGS. 1 through 10.

FIGS. 4, 8, and 10 have been amended herein. Specifically, FIGS. 4, 8, and 10 have been revised to delete the term "treatbin" from each figure. No new matter has been added.

REMARKS

The Office Action mailed March 31, 2005 has been received and reviewed. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. The amendments do not surrender any scope of any claim as originally filed. No new matter has been entered. Claims 1-20 are pending in the application. All stand rejected. Reconsideration is respectfully requested.

1. Claims 1-17 and 35 U.S.C. § 112, 1st ¶

Claims 1-17 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement and failing to comply with the written description requirement. Specifically, it was thought that the specification does not reasonably provide enablement for a method of administering functional parts, derivatives, and/or analogues of IFN-β. Regarding the "functional part," the Examiner asserts that what makes up the part of IFN-β responsible for post-ischaemic activity is not disclosed or known in the art. Regarding derivatives and/or analogues, the Examiner asserts that applicants have not further defined what these molecules may encompass. The Examiner further asserts that in some situations the alteration of a single amino acid or nucleotide in a protein can alter the function or activity of a protein, and therefore, that could be the case with IFN-β. Regarding claim 17, the Examiner asserts that claim 17 reads on preventing cell death in a single cell as well preventing cell death in every cell. The rejection based upon the written description requirement was grounded on the same reasoning as the enablement rejection. Specifically, it was thought that it was not clear what region of the protein was responsible for activity. It was also thought that one of ordinary skill in the art cannot envision the detailed chemical structure of the encompassed genus of polypeptides to be used in the claimed invention. Applicants respectfully traverse these rejections.

Applicants respectfully submit that Interferons are a long studied group of proteins of which much is known. One of ordinary skill in the art is well aware of the functional parts, suitable derivatives, and analogues of IFN-β. Interferon-beta (IFN-β) belongs to the type 1 IFN family. Members of this family include 13 IFN-α subtypes, IFN-β, IFN-ω, and IFN-τ. Antiviral activity led to the name 'interferon' and still serves to define the unit of IFN activity. However,

type 1 IFNs also have anti-proliferative, immunomodulatory, and other activities. All human type 1 IFN genes are clustered in the same chromosomal region, on the short arm of chromosome 9. A dendogram constructed on basis of a Njplot profile revealed that IFN-α subtypes, IFN-β, IFN-ω, and IFN-τ fall into one cluster, indicating that all type 1 IFNs are closely related. Type 1 IFNs differ, with respect to N-glycosylation sites, with those present in IFN-β. However, the sugar moiety was found to be neither structurally nor functionally relevant. All type 1 IFNs are acid-stable to pH 2 and heat-stable. Three-dimensional models suggest that the globular structure of type 1 IFNs consists of a bundle of five alpha-helices, which form two polypeptide domains. Disulfide bond Cys29-Cys139 stabilizes both domains in a bioactive configuration. The IFN molecule exerts its functional entity only as an organic polypeptide complex and therefore molecular fragments apparently lack biological activity. All type 1 IFNs have overlapping functions and bind to the same cell surface receptor, a fact implying a high structural conservation of their receptor-binding areas. All type 1 interferons (interferon-alpha, interferon beta, interferon-omega, hybrids and consensus version thereof) share a common receptor through which their effects are mediated (*i.e.*, composed of the alpha/beta interferon receptor IFNAR-1 and IFNAR-2 chains (Uze et al., 1990, Cell 60, 225-234; Novick et al., 1994, Cell 77, 391-400; Domanski et al., 1995, J. Biol. Chem. 270, 21606-21611). These facts are all well-known to those of ordinary skill in the art. One of ordinary skill in the art can rely of a large body of interferon art to produce many different derivatives or analogues of interferon-β. It is therefore respectfully submitted that one of ordinary skill in the art is not presented with an undue burden for selecting a suitable analogue. Additionally, below are specific examples of IFN-β derivatives and analogues.

For instance, a number of recombinant IFN-β proteins have been approved for the treatment of multiple sclerosis, a glycosylated form with the predicted natural amino acid sequence (IFN-β-1a) and a non-glycosylated form that has a Met-1 deletion and a Cys-17 to Ser mutation (IFN-β-1b). This latter IFN-β protein is also called rIFN-β-Ser or Betaseron. IFN-β-lb is both a derivative of human IFN-β, where serine was genetically engineered to substitute for cysteine at position 17 and is produced in *E. coli*, and a part of human IFN-β, *i.e.*, a part without the glycosylation of human IFN-β. The site-specific substitution was made to obtain a product

that is more stable upon storage. IFN-β-lb has been shown to have the same panel of biological activities as glycosylated native IFN-β and IFN-β-1a. (Runkel et al. 1998). Thus, non-glycosylated IFN-β is both a functional derivative and a functional part of IFN-β.

Applicants respectfully submit that Interferon alfacon-1 (also referred to as consensus IFN) is a synthetic recombinant type-1 IFN developed by comparing the amino acid sequences of several natural IFN-α subtypes and assigning the most frequently observed amino acid in each corresponding position to generate a consensus molecule. This consensus IFN binds with high affinity to the type 1 IFN receptor and has greater biological activity than naturally occurring IFN-alpha subtypes. (Koyama et al. 1999). One of ordinary skill in the art can thus produce interferons with no counterpart in nature. It is therefore respectfully submitted that one of ordinary skill in the art knows how to produce analogues of IFN-β.

The rejection with respect to claim 17 relating to "at least in part preventing cell death" is rendered moot with the amendment to claim 17.

Regarding enablement, the above explanation clearly shows that a person of ordinary skill in the art would be able to practice the invention commensurate in scope with the claims without undue experimentation. Therefore, claims 1-17 are enabled.

Applicants respectfully submit that the specification provides adequate written description for a method of administering a functional part, derivative, and/or analogues of IFN-β. The Specification provides a description of functional part, derivatives, and/or analogues on page 8 line 21 till page 9, line 13. Applicants note that the structure of claimed compounds is not required to satisfy the written description requirement. M.P.E.P. § 2163(a)(ii) provides that "[t]he written description requirement for a claimed genus may be satisfied by . . . functional characteristics coupled with a known or disclosed correlation between function and structure . . . sufficient to show the applicant was in possession of the invention." The above discussion clearly shows functional derivatives of IFN-β and a known method for developing an analogue. Given the abundant knowledge in the interferon art, applicants are clearly in possession of the claimed uses of the functional part, derivative, and analogues of IFN-β. Therefore, applicants have satisfied the written description requirement.

2. Claims 1-17 and 35 U.S.C. § 112, 2nd ¶

Claims 1-17 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being incomplete for omitting essential steps. Claims 1-15 stand rejected as being indefinite. Regarding the omitted steps specifically, it was thought that the omitted steps are: how applicants plans to identify patients suffering from H/I related blood flow resistance and how outcomes are to be measured. Regarding indefiniteness specifically, it was thought that because there is no recited measurable outcomes, then "suitable dose" and "therapeutic dose" are indefinite. Applicants respectfully traverse these rejections.

Applicants respectfully submit that H/I related blood flow resistance is a problem in a variety of human diseases (page 1, line 26-27 description), one of which is traumatic brain injury (page 5, line 29 description). Other situations wherein H/I related blood flow resistance occurs are: a person has not been able to breathe oxygen for a limited amount of time (page 2, line 24-27 description); in surgery one or more parts of the body may suffer from reduced blood flow due to isolation from the circulation (page 2, line 19-20 description); in organ transplantation (page 3-4 lines 30 and 1-3). Physicians are familiar with hypoxia and ischaemia situations. Physicians are also the appropriate person to identify the presence of a disorder in which this resistance occurs. He or she will be able to do that as there are methods available to identify patients with hypoxia or ischaemia. How to identify patients suffering from H/I related blood flow resistance is known in the art. Additionally, for a step to be "essential" it must be "disclosed to be essential to the invention as described in the specification or in other statements of record." *See* M.P.E.P. § 2173.01. The Examiner has not provided any "statements of record" that the above referenced steps are essential to the claimed invention. Therefore, claims 1-17 are not incomplete for omitting essential matter.

Applicants also submit that the physician will furthermore be able to establish whether the condition of a patient improves. The specification further provides adequate guidance for the person skilled in the art to arrive at an effective dose, both in the examples and in the description (page 9, lines 15-22; page 11, lines 15-17). Therefore, claims 1-15 are not indefinite.

3. Claims 1-17 and 35 U.S.C. § 103(a)

Claims 1-17 stand rejected under 35 U.S.C. § 103(a) as assertedly being obvious in light of Wee Yong *et al.* in view of Boyle *et al.* and Saikumar *et al.* Specifically, it was thought that Wee Yong *et al.* teaches that IFN-β is immunosuppressive and possesses various anti-inflammatory properties, but that Wee Yong *et al.* does not teach the use of IFN-β to treat hypoxia/ischaemia (H/I) related blood flow resistance. It was also thought that Boyle *et al.* teaches that H/I related blood flow resistance is an inflammatory process and anti-adhesion molecule therapy is effective. It was also thought that Saikumar *et al.* teaches that the inflammatory process is responsible for cell death as a result of H/I. The Examiner asserts that it would have been obvious to use IFN-β to treat H/I related blood flow resistance, including treating the resulting cell death, because H/I related blood flow resistance and cell death are inflammatory process and IFN-β has anti-inflammatory properties. The Examiner also thought that there is no indication in the art that H/I is markedly different in various parts of an organism. The Examiner asserted that therefore IFN-β would be expected to be effective in the brain, heart, limbs, or transplanted organs because the results of H/I are the same in those organs. Applicants respectfully traverse this rejection.

Applicants respectfully submit that Interferon has many properties of which an anti-inflammatory property is only one. Even if one would decide that an anti-inflammatory property is an essential quality for a method for the treatment of H/I related blood flow resistance, one's choice would not likely be interferon. There are very many anti-inflammatory drugs, of which many have a far stronger anti-inflammatory effect then interferon. The mere fact that a compound has an anti-inflammatory effect does not make it suitable for a method of the invention.

For example, it is well known in the art that corticosteroids are among the most potent and widely used anti-inflammatory drugs. Members of this class of drugs would be a much more likely choice if one had the intention to treat the putative inflammatory component of the cascade leading to cell death after an H/I related blood flow resistance. Several members of this well-known class of inflammatory drugs have been tested, in several dosages. Even in human trials, none of the most potent and well-known inflammatory drugs known to man proved beneficial.

(Cochrane Database Syst Rev 2000;(2):C0000064; Br Med J 1978 Oct 7;2(6143):994-6; Br Med (Clin Res Ed) 1986 Jan 4;292(6512):21-3; Br Med 3 1976 Dec 11;2(6049):1409-10).

Moreover, a trial with Enlimolab, a drug with putative inflammatory properties even more closely related to the putative mechanism of the current invention, turned out to be detrimental. (Neurology 2001 Oct 23;57(8):1428-34; Neurology 1997; 48 (Suppl): A270).

Thus, one of ordinary skill in the art is confronted with much art that proves that anti-inflammatory drugs are not effective in H/I related blood flow resistance. One of ordinary skill in the art thus has no reasonable expectation of success of IFN-β in that treatment. There is nothing in the art that would suggest that IFN-β would have a better chance than the anti-inflammatory drugs tested.

Applicants also note that even if the effects of H/I in different organs are the same, it is does not necessarily follow that H/I will be effective in all organs. By way of example only, as will be discussed below, endothelial cells differ in different parts of an organism. Therefore, one of ordinary skill in the art would not assume that just because H/I is effective in one organ, it will be effective in all organs.

It is therefore respectfully submitted that the use of IFN-β or functional parts, derivatives, and/or analogues thereof for the treatment of H/I related blood flow resistance is not obvious. It was rather an unlikely choice considering its properties known in the art. Withdrawal of the rejection is thus requested.

4. Claims 1-17 and 35 U.S.C. § 102(b)

Claims 1-17 are rejected on two grounds. Claims 1-17 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by EP 0 797 998 A1 ("Sano *et al.*"). Specifically, it was asserted that Sano *et al.* teach a method of using IFN-β to treat cardiovascular diseases and/or complications. The types of cardiovascular diseases and/or complications include: brain and heart infarction, ischaemic vascular disorders, blood flow insufficiency, vascular restenosis, and vascular disorders related to inflammatory processes. It was also asserted that Sano *et al.* teach the method may be used to treat necrosis as a result of angitis, which leads to "clot formation" and "aneurysm formation." Applicants respectfully traverse the rejection.

Applicants respectfully submit that Sano *et al.* is directed toward the protection of endothelial cells as a direct effect. The present invention treats H/I related blood flow resistance. Thus, Sano *et al.* is not directed towards the subject matter of the present invention. Sano *et al.* is concerned with the protection of endothelial cells. Endothelial cells can be derived from varying sources. The endothelial cells that Sano *et al.* used in their experiments were umbilical vein endothelial cells. It is not possible to extrapolate results obtained in umbilical cord endothelial cells to cells from other sources. Applicants assert, that it is well known in the art, for example, that umbilical vein endothelium is very different from brain endothelium (J Neuroimmunol. 1998 Aug 1;88(l-2):13-20; J Neurovirol. 2000 May;6 Suppl 2:S47-51; J Neuroimmunol. 1995 Jul;60(1-2):99-106; J Neuroimmunol. 1996 Dec;71(l-2):215-22; Neurochem Int 1997, 30(4-5):449-53); Arterioscler Thromb Vasc Biol. 1997 Jul;17(7):1193-202). Moreover, Sano *et al.* do not show any other data than those derived from the mentioned endothelial cells in culture.

Moreover, the claims recite "administering to an/the individual." Sano *et al.* does not perform "administering to an individual." Sano *et al.* only presents experiments *in vitro*. Sano *et al.* does not describe each and every element of the claims, and therefore does not anticipate the claims. *See* Verdegaal Brothers v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). It is requested that the Examiner maintain the same standard for enablement for the present invention and the art. The present invention provides *in vivo* data on the effectiveness of IFN-β for the purpose of treating H/I related blood flow resistance. Sano *et al.* presents only *in vitro* data and extrapolates from these results. If the Examiner considers the present invention not enabled over the full *in vivo* scope as result of lack of experimental support, then surely Sano *et al.* cannot be enabled at all.

Claims 1-17 also stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by JP 09151337 ("Sano"). Specifically it was asserted that Sano teaches a method of using IFN-β in the transplantation of organs and to treat various cardiovascular conditions, including restenosis after PTCA, intima hyperplasia after arteriosclerosis, and vasculitis in artery occlusion. It was also asserted that the method taught by Sano would inherently be effective for reducing cell death following H/I because, for example, a method directed to treating restenosis following

PTCA would inherently, whether appreciated or not, decrease cell death as a result of treating restenosis. Applicants respectfully traverse the rejection.

Applicants respectfully submit that Sano is concerned with multiplication of smooth muscle cells. Inhibiting multiplication of smooth muscle cells is not an element of the claimed inventions. Additionally, muscle cell proliferation is a process of weeks. The present invention assesses H/I related blood flow resistance. This resistance is observed shortly after removal of the primary cause. H/I related blood flow resistance is a phenomenon of the microvascular system, *i.e.*, of capillary vessels that do not have smooth muscle cells. H/I related blood flow resistance is thus independent of smooth muscle cell proliferation. Administration of interferon in a method of the invention is thus performed for a different part of the vascular system and with a different purpose.

Claims 1-17 are not anticipated by Sano *et al.* or Sano.

If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

Kelly A. Echols
Registration No. 55,911
Agent for Applicants
TRASKBRITT, P.C.
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

Date: August 26, 2005
KAE/bv

Enclosures: Appendix A including
Replacement Sheets
Annotated Sheets Showing Changes

\\Traskbritt1\Shared\DOCS\2183-6139US\127214.doc